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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,932	07/29/2002	Frank Luyten	522-1783	1230

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EXAMINER	
WOOD, AMANDA P	
ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,932	LUYTEN ET AL.	
	Examiner	Art Unit	
	Amanda P. Wood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-36,39-41,43-47 and 49-59* is/are pending in the application.

4a) Of the above claim(s) *29,30,39-41,46,47,49,50 and 52-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36,43-45,51 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04, 4/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II (claims 31-32, 43 and 45) in the reply filed on 6 February 2006 is acknowledged.

Amended claims 33-36, 44, and 51 have been rejoined to Group II. New claims 55-59 have been entered and joined to Group II.

Claims 31-36, 43-45, 51, and 55-59 are presented for examination on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 34, 36, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Quarto et al (Endocrinology 1997).

Quarto et al teach a method of determining the expression of positive and negative markers of chondrocyte phenotypic stability comprising the steps of: a) providing a suspension of isolated or expanded chondrocytes and determining a

positive or negative marker thereof, b) injecting intramuscularly or subcutaneously in a non-human animal said suspension in an iso-osmotic liquid comprising articular chondrocytes in an amount equivalent to at least 1 x 10^6 chondrocytes as applied to nude mice (i.e., immune-deficient mice), c) allowing the formation of cartilaginous tissue, d) sacrificing the animal, e) evaluating the in vivo formed cartilage histologically for stable, non-vascularized cartilage, and f) identifying a positive or negative molecular marker of the isolated or expanded cells which formed stable, non-vascularized cartilage in vivo. Quarto et al further teach that the chondrocytes can be obtained from a cartilage biopsy, such as from chick embryo tibiae, a primary culture can be established, and the chondrocytes can then be expanded before injection or transplantation into nude mice (see, for example, pg. 4967, col. 1 and 2). In addition, Quarto et al teach that positive markers, such as type I and II collagens (i.e., positive markers co-detectable with BMP-2 or FGFR-3), and negative markers, such as type X collagen (i.e., a negative marker co-detectable with ALK-1), can be detected using antibodies against those markers (see, for example, pg. 4967, col. 1). Furthermore, Quarto et al teach that a graft comprising an expanded population of stable chondrocytes can be implanted into a mammal (i.e., a patient) such as a nude mouse, using devices such as porous hydroxyapatite ceramic tubes or hemostatic sponges of bovine collagen (see, for example, pg. 4967, col. 2).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-36, 43-45, 51, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quarto et al in view of Kolettas et al (Journal of Cell Science 1995).

Quarto et al is relied upon for the reasons set forth above.

Quarto et al do not expressly teach a method wherein mRNA from chondrocytes is hybridized to DNA probes for positive markers for chondrocyte phenotypic stability.

Kolettas et al beneficially teach that chondrocytes obtained from a cartilage biopsy expressed markers at mRNA and protein levels considered characteristic of cartilage (i.e., positive markers and/or markers co-detectable with positive markers) for chondrocyte phenotypic stability), such as types I, II and IX collagens. Furthermore, Kolettas et al beneficially teach a method wherein mRNA from cultured cells was extracted and hybridization performed using labeled cDNA probes for both positive markers (i.e., types I, II and IX collagens) and negative markers, such as type X collagen (see for example, pg. 1992, col. 1 and 2).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Quarto et al based upon the beneficial teachings provided by Kolettas et al, with respect to the art-recognized method of identifying cells having a particular marker using DNA

hybridization, as discussed above. Furthermore, the Quarto et al particularly point out that chondrocytes can be biopsied, cultured, and expanded, then injected or grafted into an animal or patient, and the resulting cartilaginous tissue analyzed for markers indicating chondrocyte phenotypic stability, such as type II collagen (i.e., a marker co-detectable with BMP-2 or FGFR-3), or for markers indicating chondrocyte phenotypic instability, such as type X collagen (i.e., a marker co-detectable with ALK-1), and therefore, it would have been obvious and beneficial for the skilled artisan to use the methods taught by Quarto et al so as to determine whether chondrocytes are phenotypically stable, based upon the particular positive and negative markers detected on those cells. In addition, Kolettas et al particularly point out that it is possible to use DNA hybridization to determine whether mRNA of particular markers (i.e., positive and negative markers for chondrocyte phenotypic stability) are present in a population of expanded or isolated chondrocytes. Furthermore, it would have been obvious to one of ordinary skill in the art at he time the claimed invention was made to develop a therapeutic composition for humans comprising cells identified as phenotypically stable chondrocytes in at least a pharmaceutically acceptable carrier and/or a growth factor, based upon the beneficial teachings of Quarto et al, wherein a composition of chondrocytes and growth factors was injected into nude mice, and allowed to form cartilage which was subsequently verified histologically as cartilaginous tissue. The result-effective adjustment of particular conventional working conditions (e.g., choosing a particular positive or negative marker to identify, and/or using a particular means of determining the presence of a marker mRNA, such as DNA arrays or chips, Northern

hybridization, or RT-PCR) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Claims 56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quarto et al in view of Kolettas et al, as applied to claims 31-36, 43-45, 51, and 55 above, and further in view of Si et al (Eur. J. Oral Sci. 1997-Abstract only available).

Quarto et al and Kolettas et al are relied upon for the reasons set forth above.

Quarto et al and Kolettas et al do not expressly teach a method comprising determining expression of a positive marker of chondrocyte phenotypic stability, wherein the positive marker is BMP-2.

Si et al beneficially teach that chondroblasts, in early chondrogenesis, and chondrocytes express high levels of BMP-2 mRNA, and that BMP-2 expression is correlated with the differentiation of mesenchymal cells into chondrocytes (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Quarto et al based

upon the beneficial teachings provided by Kolettas et al, with respect to the art-recognized method of identifying cells having a particular marker using DNA hybridization, and by Si et al, with respect to the finding that BMP-2 mRNA is expressed at high levels in chondrocytes and is correlated with differentiation of mesenchymal cells into chondrocytes, as discussed above. Furthermore, the Quarto et al particularly point out that chondrocytes can be biopsied, cultured, and expanded, then injected or grafted into an animal or patient, and the resulting cartilaginous tissue analyzed for markers indicating chondrocyte phenotypic stability, such as type II collagen (i.e., a marker co-detectable with BMP-2 or FGFR-3), or for markers indicating chondrocyte phenotypic instability, such as type X collagen (i.e., a marker co-detectable with ALK-1), and therefore, it would have been obvious and beneficial for the skilled artisan to use the methods taught by Quarto et al so as to determine whether chondrocytes are phenotypically stable, based upon the particular positive and negative markers detected on those cells. In addition, Kolettas et al particularly point out that it is possible to use DNA hybridization to determine whether mRNA of particular markers (i.e., positive and negative markers for chondrocyte phenotypic stability) are present in a population of expanded or isolated chondrocytes. Furthermore, it would have been obvious to one of ordinary skill in the art at he time the claimed invention was made to develop a therapeutic composition for humans comprising cells identified as phenotypically stable chondrocytes in at least a pharmaceutically acceptable carrier and/or a growth factor, based upon the beneficial teachings of Quarto et al, wherein a composition of chondrocytes and growth factors was injected into nude mice, and allowed to form

cartilage which was subsequently verified histologically as cartilaginous tissue. The result-effective adjustment of particular conventional working conditions (e.g., choosing a particular positive or negative marker to identify, and/or using a particular means of determining the presence of a marker mRNA, such as DNA arrays or chips, Northern hybridization, or RT-PCR) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Claims 57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quarto et al in view of Kolettas et al and Si et al, as applied to claims 31-36, 43-45, 51, and 55-56 and 58 above, and further in view of Hamada et al (J. Bone Miner. Metab. 1999).

Quarto et al, Kolettas et al, and Si et al are relied upon for the reasons set forth above.

Quarto et al, Kolettas et al, and Si et al do not expressly teach a method comprising determining expression of a positive marker of chondrocyte phenotypic stability, wherein the positive marker is FGFR-3.

Hamada et al beneficially teach that FGFR-3 mRNA is expressed, along with aggrecan and type II collagen, by rat condylar and tibial chondrocytes. Furthermore, Hamada et al report that FGFR-3 has been found in the proliferating and hypertrophic zones of the tibial cartilage of human embryos.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Quarto et al based upon the beneficial teachings provided by Kolettas et al, with respect to the art-recognized method of identifying cells having a particular marker using DNA hybridization, by Si et al, with respect to the finding that BMP-2 mRNA is expressed at high levels in chondrocytes, and by Hamada et al, with respect to the finding that FGFR-3 mRNA is expressed in chondrocytes, as discussed above. Furthermore, the Quarto et al particularly point out that chondrocytes can be biopsied, cultured, and expanded, then injected or grafted into an animal or patient, and the resulting cartilaginous tissue analyzed for markers indicating chondrocyte phenotypic stability, such as type II collagen (i.e., a positive marker co-detectable with BMP-2 or FGFR-3), or for markers indicating chondrocyte phenotypic instability, such as type X collagen (i.e., a marker co-detectable with ALK-1), and therefore, it would have been obvious and beneficial for the skilled artisan to use the methods taught by Quarto et al so as to determine whether chondrocytes are phenotypically stable, based upon the particular positive and negative markers detected on those cells. In addition, Hamada et al and Si et al particularly point out that FGFR-3 and BMP-2 mRNA are both expressed in chondrocytes, particularly early in chondrogenesis by chondrocytes. In addition, Kolettas et al particularly point

out that it is possible to use DNA hybridization and RT-PCR to determine whether mRNA of particular markers (i.e., positive and negative markers for chondrocyte phenotypic stability) are present in a population of expanded or isolated chondrocytes. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to develop a therapeutic composition for humans comprising cells identified as phenotypically stable chondrocytes in at least a pharmaceutically acceptable carrier and/or a growth factor, based upon the beneficial teachings of Quarto et al, wherein a composition of chondrocytes and growth factors was injected into nude mice, and allowed to form cartilage which was subsequently verified histologically as cartilaginous tissue. The result-effective adjustment of particular conventional working conditions (e.g., choosing a particular positive or negative marker to identify, and/or using a particular means of determining the presence of a marker mRNA, such as DNA arrays or chips, Northern hybridization, or RT-PCR) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

APW
Examiner
Art Unit 1655

APW

CHRISTOPHER R. TATE
PRIMARY EXAMINER